UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/517,565	12/07/2004	Joel Moss	4239-64830-06	9987

36218 7590 06/12/2007

KLARQUIST SPARKMAN, LLP
121 S.W. SALMON STREET
SUITE #1600
PORTLAND, OR 97204-2988

EXAMINER	
MAASHO, KERIMA K	
ART UNIT	**PAPER NUMBER**
1609	
MAIL DATE	**DELIVERY MODE**
06/12/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/517,565	MOSS ET AL.	
	Examiner	Art Unit	
	Kerima Maasho	1609	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12 and 19-35* is/are pending in the application.

4a) Of the above claim(s) *13-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,19-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 December 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :12/07/2004, 01/06/2005, 05/22/2006,10/02/2006.

Detailed action

Applicant's election of group I with traverse filed on 05/14/2007 is acknowledged. The elected group I is drawn to method of producing a protein with an increased activity or stability, a composition comprising a polypeptide, a method of increasing the activity or stability of a defensin polypeptide and a method of increasing an immune response by administering a defensin polypeptide.

The applicants' argument that the groups relate to a single general inventive concept is not convincing. Group II relates to a method determining if a protein can be stabilized or if an arginine residue in the protein is capable of being ADP-ribosylated. Group I and II contain different methods with different steps, objectives and effects and accordingly do not have the same special technical features. The current amendment of claim 13 by inserting "*the replacement of an arginine residue capable of being ADP-ribosylated with a tryptophan residue or a phenylalanine residue in order to increase the activity or stability of a protein*" does not fix the issue as the claim still relates to a method of determining if a protein can be stabilized or the arginine residue in the protein is capable of being ADP-ribosylated. The objective of this method is indeed different from that of group I wherein the method of producing a protein with increased activity or stability is really different from a method of determining if the protein can be stabilized or a residue capable of being ribosylated, as such this would require different steps and outcome.

Therefore, the amended claim does not fix the lack of a special technical feature shared among the claims in groups I and II as to form a single general inventive concept therefore the restriction requirement is maintained and group I will be examined in this application.

The applicants' traversal of the species election is acknowledged. The claims reciting the species depend from a very broad claim and depending on which protein is used in the method, the substitution may not possess each of the 3 antimicrobial activities. Claims 1 and 19 are so broad as to include a huge number of different proteins and polypeptides with different biological activities thus the resulting immune response may be different from the claimed ones. Examiner agrees with the applicants that the measurement of T cell chemotaxis, neutrophil recruitment, or cytokine release are very well known assays in the art, however the claimed invention in claims 3, 23, is not for the measurement of the activity of such cells but rather that the claimed antimicrobial activity comprises of T cell chemotaxis, neutrophil recruitment, or cytokine release. Therefore, the imposed species election is maintained and T cells as elected species will be examined in the present application.

Claims 1-35 are pending. Restriction/election was made with traverse in the reply filed on 05/14/2007, however the requirement for restriction/election is maintained as explained above. Accordingly claims 13-18 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicants elected T cells as the species for the

antimicrobial activity and neutrophil. Claims 1-12, and 19-35 are under consideration for further examination.

Objection

1. Claims 20-21 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 20 does not further limit claim 21 and likewise claim 21 does not further limit claim 20. Therefore, in the interest of compact prosecution, claims 20 and 21 have been treated as if they depended from claim 19. However, this treatment does not relieve applicant of the burden of responding to this objection.

Claim Rejections - 35 USC § 112, 2nd paragraph rejections

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

2. Claims 1-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite because it does not convey that the substitution is directly related to the increased activity or stability. The phrase 'thereby producing the protein with increased activity or stability" should be changed to "wherein the substitution increases the activity or stability of said protein".

Claims 1, 19, and 29, refer to "increased activity or stability", it is not clear what type of increased activity or stability the claim refers. The language of these claims is vague and indefinite and the metes and bounds of the invention are not clear. While the specification can be used to provide definitive support, the claims are not read in a vacuum. Rather, the claim must be definite and complete in and of itself. Limitations from the specification will not be read into the claims. The claims as they stand are incomplete and fail to provide adequate structural properties to allow for one to identify what is being claimed. The type of activity or stability in the last line of the claims is critical to the methods.

Claims 1, 13, 15, 19, 29 and 33 use the term "capable of being ADP-Ribosylated" but do not actually require the arginine to be ADP-ribosylated for substitution in the claimed structure, e.g., having the capability is not the same as performing the function. Is the ADP-ribosylation a requirement for substitution of the arginine with Trp or Phe residues? A definitive recitation of the claim is required. For e.g. Claim 26 positively recites a specific protein comprising at least one arginine residue substituted by a Trp or Phe residue.

Claims 2-12, 14, 16-18, 20-28, 30-32 and 34-35 are also indefinite insofar as they depend from claims 1, 13, 15, 19, 29 and 33.

Claim Rejections - 35 USC § 112, 1st paragraph rejections

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-12 and 33-34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. While replacement of amino acid residues in proteins have been used to alter or enhance biological function the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. Additionally, the claims are not enabled for a method of increasing an immune response in a subject by administering the substituted amino acid of defensin polypeptide wherein the subject has *any* immune disorder.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G)

The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims: In the instant case applicants broadly claim in claim 1 a protein, which encompasses ANY protein with an increased activity or stability comprising replacing arginine residue with a tryptophan or phenylalanine residue.

Since all proteins do not behave the same upon alterations, selective point mutation to one key residue could eliminate the function of the polypeptide while it could enhance the activity in some. If the range of decreased binding ability after single point mutation of a protein antigen varies, one could expect point mutations in the protein antigen to cause varying degrees of loss of protection/function, depending on the relative importance to the binding interaction of the altered residue. Alternatively, the combined effects of multiple changes in an antigenic determinant could again result in loss of function. A protein having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new protein that is precipitously or progressively unrecognizable from its former state. Applicants have provided no guidance to enable one of ordinary skill in the art how to determine, without undue experimentation, the effects of different amino acid substitutions and the nature and extent of the changes that can be made and predict what the resultant activity will be, e.g., whether it will result in increased neutrophil recruitment, etc.. It is expensive and time consuming to make amino acid substitutions at more than one position, in a particular region of the protein, in view of the many fold possibilities for change in structure and the uncertainty as to what utility will be possessed.

The state of predictability in the art: Mikayama et al. (Proc.Natl.Acad.Sci. USA, 1993. vol. 90: pp 10056-10060) which teaches that the three-dimensional structure of molecules is important for their biological function and even a single amino acid difference may account for markedly different biological activities.

The state of prior art: Rudinger et al. (Peptide Hormones Biol Council 1976, pp 5-7) teach that amino acids owe their 'significance' to their inclusion in a pattern which is directly involved in recognition by, and binding to, the receptor and the significance of the particular amino acids and sequences for different amino acids cannot be predicted *a priori*, but must be determined from case to case by painstaking experimental study. Given the lack of guidance contained in the specification regarding the location of acceptable amino acid substitutions, and their specific location within the polypeptide relating to a specific activity (e.g., increased neutrophil recruitment, etc.) one of skill in the art could not make or use the broadly claimed invention without undue experimentation.

Claims 33-34 contain subject matter which was not described in the specification in such a way to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. The claim language is so broad that it encompasses modifying immune response in ANY subject with ANY immune disorder. While defensin could play a role in a variety of immune disorders, it exacerbates some autoimmune disorders such as artherosclerosis. Higazi et al (Blood, 1997, vol 89, pp4290-98) teach that defensin released from activated or scenescent neutrophils may contribute to the localization and

persistence of lipoprotein (a) in human vessels and thereby predispose to the development of atherosclerosis (see abstract, p 4290).

Considering the broad scope of the above claims, the limited teaching in the specification, and the state of the art, it is concluded that undue experimentation would be required to enable the full scope of the invention as claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1, 2, 5, 7-9 19-22, 24, are rejected as under 35 U.S.C. 102(b) as being anticipated by Svendsen et al (US 2003/0148936).

Claim 1 refers to a method of producing a protein with an increased acitivity or stability comprising replacing an arginine with a tryptophan or phenylalanine residue. Claim 2 refers to the antimicrobial activity, wherein the protein is a defensin (claim 5). Claim 7 refers to the method wherein the arginine residue is substituted with a

tryptophan and claim 8 with a phenylalanine residue. Claim 9 refers to the increased activity with the substitutions as compared to a polypeptide having an arginine residue in the amino acid sequence of the protein. Claims 19-22 refer to a composition comprising a polypeptide comprising an amino acid wherein at least one residue of arginine is substituted with a tryptophan or phenylalaonine residue; wherein the substitution increases the activity or stability of the polypeptide (claim 19), with an antimicrobial activity (claim 20), wherein the arginine residue is substituted with a tryptophan (claim 21) and phenylalanine (claim 22). Claim 24 refers to the composition wherein the protein is a defensin. Claim 26 refers to

Svendsen et al teach antimicrobial proteins and peptides which have been modified to enhance cytolytic activity [0001-0002]. In addition Svendsen et al teach pharmaceutical compositions containing these peptides, and their use as medicaments, particularly as antibacterial or antitumor agents (p 7, [0062]). Svendsen et al further teach that peptides encorporating lipophilic amino acid such as tryptophan and phenylalanine will preferably exhibit an enhanced cytotoxic effect against bacterial or tumor cells (p 1, [0008-0010]). Svendsen et al further teach that increased bioactivity was as a result of a serendipitous transfer of Pmc from arginine to tryptophan, amino acids such as Trp, which carry the protecting group can be synthesized directly and incorporated into the peptide (p 3, [0018]). Svendsen et al further teach that suitable peptides, which can be modified to provide peptides with enhanced activity, include all peptides such as magainins, cecropins, defensins and others that are known in their unmodified form to exhibit antimicrobial activity (p 4, [0031]). In addition Svendsen et al

teach substitution for the native peptide and a number of modified peptides wherein single amino acid substitutions for tryptophan or phenylalanine at positions 16 or 19 have been made, with a resulting increase in antibacterial activity (p 21, [0280], and table 7].

Therefore, Svendsen et al meets every limitation of the above claims of the present invention. Although, Svendsen et al do not mention whether the arginine residue of their teaching is capable of being ADP-ribosylated the outcome of replacing arginine residue with tryptophan or phenylalanine resulted in the same property as the present invention, e.g., the increased antimicrobial activity in peptides. Accordingly, it appears that the peptides of Svendsen are inherently capable of being ADP-ribosylated. The Patent Office does not have the facilities to manufacture products and conduct comparisons between products made by applicant's methods or prior art methods. Therefore the burden is shifted to applicant, who does have such facilities. See In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977) [PTO can require an applicant to establish that a prior art product does not necessarily possess the characteristics of the claimed product when the prior art and claimed products are identical or substantially identical.]

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1-3, 5-9, 19-35 are rejected as under 35 U.S.C. 103(a) as being unpatentable over Svendsen et al (US 2003/0148936) further in view of (Paone et al (provided in the IDS filed on 01/06/2005).

Claims 1, 2, 5, 7-9 19-22, and 24 refer to the method of producing a protein with increased activity as above. Claim 6 refers to the method wherein the protein is an alpha defensin. Claims 19-25 refer to a composition comprising a polypeptide with antimicrobial activity wherein the arginine residues is substituted with a tryptophan and phenylalanine, wherein the antimicrobial activity comprises chemotaxis of T cells and

the protein is defensin. Claims 26-28 refer to a pharmaceutical composition and claims 29-32 refer to a method of increasing the activity of defensin. Claims 33-35 refer to a method of increasing immune response in a subject, wherein the response comprises of T cell chemotaxis and the subject has immune disorder.

Svendsen et al teach antimicrobial proteins and peptides which have been modified to enhance cytotoxic activity [0001-0002]. In addition Svendsen et al teach pharmaceutical compositions containing these peptides, and their use as medicaments, particularly as antibacterial or antitumor agents. Svendsen et al further teach that peptides encorporating lipophilic amino acid such as tryptophan and phenylalanine will preferably exhibit an enhanced cytotoxic effect against bacterial or tumor cells (p 1, [0008-0010]). Svendsen et al further teach that increased bioactivity was as a result of a serendipitous transfer of Pmc from arginine to tryptophan, amino acids such as Trp, which carry the protecting group can be synthesized directly and incorporated into the peptide (p 3, [0018-0010]). Svendsen et al further teach that suitable peptides, which can be modified to provide peptides with enhanced activity, include all peptides such as magainins, cecropins, defensins and others that are known in their unmodified form to exhibit antimicrobial activity (p 4, [0031]). In addition Svendsen et al teach substitution for the native peptide and a number of modified peptides wherein single amino acid substitutions for tryptophan or phenylalanine at positions 16 or 19 have been made, with a resulting increase in antibacterial activity (p 21 [0280] table 7]. While Svendsen et al teach arginine replacement with tryptophan or phenylalanine for increased antimicrobial

activity in magainin and lactoferrin peptides they do not specifically teach this modification in defensins nor do they emphasize the ADP-ribosylation of the arginine that is substituted for tryptophan or phenylalanine. However, they suggest that this arginine modification for enhanced activity can be done in defensins as well as other peptides that are known to exhibit antimicrobial activity in their unmodified forms.

Paone et al teach the modification of arginine residues in defensins. Paone et al further teach that the ADP-ribosylation of human neutrophil peptide-1 regulates its biological activity and that a family of ADP-ribosyl-transferases catalyzes the transfer of ADP ribose from NAD+ to arginine residues in proteins. Two of these transferases specifically modify arginine residues in proteins (p 8231). ADP-ribosylation of Arg-14 in HNP-1 yielded a molecule with unique biological properties, which could modulate defensin activity as well as T cell chemotaxis. Paone et al further suggest that ADP-ribosyl-transferases could have an important regulatory role in the innate immune response through modification of α-defensin-1 and perhaps other basic molecules, with alteration of their biological property (p 8231, abstract). While Paone et al do not teach the arginine substitution per se, they teach the modification of arginine residues by ADP-robosyl transferases to enhance their biological properties.

Taken together the above references teach the role of tryptophan in enhanced antimicrobial activity and stability that was brought about with substitution of the arginine residue to tryptophan or phenylalanine (Svendsen et al), as well as the modification of the arginine residues by the ADP transferases (Paone et al). Therefore, it would be obvious for one skilled in the art to combine the above teachings with reasonable

expectation of success. A skilled artisan would be motivated to combine the methods of the prior art teachings because it results in the enhanced peptide antimicrobial activity.

Conclusion

Claims 1-35 are rejected for reasons stated above.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kerima Maasho whose telephone number is 571-270-3055. The examiner can normally be reached on Monday-Thursday, 7:30am-5:00pm, ALT. Friday, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mary Mosher can be reached on 571-272-0906. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

JENNIFER E. GRASER
PRIMARY EXAMINER 6/7/06